**BACKGROUND**

- Bruton’s tyrosine kinase (BTK) is a member of a B-cell receptor signaling pathway implicated in the pathogenesis of a number of B-cell malignancies.
- Ibrutinib, a potent and selective BTK inhibitor, has been approved for the treatment of chronic lymphocytic leukemia (CLL) among other indications. It acts by irreversibly inhibiting BTK.

**METHODS**

- Treatment-naive subjects or those with prior experience of BTKi therapy were included. 
- Patients were assigned to one of four dose-escalation groups.
- Pharmacokinetic (PK) and pharmacodynamic (PD) evaluations were performed.
- Assessment of activity was based on standard criteria.

**RESULTS**

- ** Pharmacokinetic Profiles**
  - Mean CLIN was 57 (4/7) nM for ibritnib, 3 (100) nM for zanubrutinib, and 60 (300) nM for ibrutinib.
  - Mean IC50 values for VEC were 57 (4/7) nM, and for IBR were 3 (100) nM.
- **Pharmacodynamic Profiles**
  - Inhibition of pBTK was measured at various time points on Cycle 1 and on Cycle 2.
- **Assessment of Activity**
  - Treatment-related adverse events were observed in patients with and without BTK C481 mutations.
- **Conclusions**
  - Vecabrutinib demonstrates antitumor activity in patients with relapsed/refractory B-cell malignancies, including those with prior BTKi and/or CAR-T cell therapy experience.

**DISCUSSION**

- Vecabrutinib inhibits BTK in healthy subjects and shows favorable safety, pharmacokinetic (PK)/pharmacodynamic (PD) profiles, supporting twice-daily (BID) administration.
- The most common treatment-emergent adverse events of any grade were anemia (70%, 7/10) and lymphopenia (60%, 6/10).
- Further studies are needed to evaluate the efficacy and safety of vecabrutinib in patients with relapsed/refractory B-cell malignancies.

**ACKNOWLEDGEMENTS**

- The authors thank the patients and caregivers who participate in these studies.

**REFERENCES**

- Sutton et al. Half of chronic lymphocytic leukemia patients relapsing under ibrutinib carry BTK and PLCG2 mutations: a European research initiative on CLL (ERIC) real-world study [oral presentation]. EHA Annual Meeting; June 14-17, 2018; Stockholm, Sweden.
- Tam et al. The BTK inhibitor, Bgb-3111, is safe, tolerable, and highly active in patients with relapsed/refractory B-cell malignancies: a phase 1/2 trial of treatment-naive subjects [abstract 347]. ASH Annual Meeting; December 10-14, 2017; Atlanta, GA.
- Neuman et al. First-in-human phase 1a study of the safety, pharmacokinetics, and pharmacodynamics of the noncovalent Bruton’s tyrosine kinase inhibitor, Vecabrutinib, in B-lymphoid malignancy patients with Prior BTKi Therapy. 2018 American Society of Hematology; November 2-5, 2018; Chicago, IL.

**CONCLUSIONS**

- Vecabrutinib demonstrates antitumor activity in patients with relapsed/refractory B-cell malignancies, including those with prior BTKi and/or CAR-T cell therapy experience.

**DISCLAIMER**

- No funding or support was associated with the preparation of this manuscript.

**SUPPORTING INFORMATION**

- Table S1: Detailed Pharmacologic and Clinical Data
- Figure S1: Flowchart of Study Design
- Figure S2: Time-Course of pBTK Suppression in Whole Blood

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